REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claims 18-22 have been amended to define the invention with additional clarity. That the claims have been amended should not be taken as an indication that Applicant agrees with any position taken by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicant reserves the right to pursue claims of alternative scope or type in a continuation application.

Claims 18-22 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of the claims to remove the language ("under conditions such that") objected to by the Examiner. Reconsideration is requested.

Claims 18, 20 and 21 stand rejected under 35 USC 103 as allegedly being obvious over Clark in view of Pels et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

In rejecting the claims as obvious, the Examiner relies on Clark as teaching that steroids, including cortexolone and 17-hydroxyprogesterone, are useful in

inhibiting angiogenesis. The Examiner acknowledges that Clark does not teach that the angiostatic steroids are useful in reducing atherosclerotic plaque. The Examiner contends, however, that Pels et al cures this deficiency by allegedly teaching that angiogenesis is "important in the pathogenesis of atherosclerotic plaque".

The Examiner concludes that the combination of Clark and Pels et al would have made it obvious to employ cortexolone and 17-hydroxyprogesterone in a method of reducing atherosclerotic plaques since angiogenesis is allegedly "known to facilitate the accumulation of atherosclerotic plaques". Applicant respectfully disagrees.

Clark teaches at column 3, lines 47 and 48, that "angiostatic steroids are useful in preventing and treating any ocular neovascularization"... (emphasis added). In Example 4 (column 6), Clark describes the inhibition of angiogenesis in a rabbit corneal neovascularization model using two angiostatic steroids. Clark does not teach, nor would it have suggested, that the results obtained had relevance in a non-ocular setting.

As indicated above, the Examiner relies on Pels et al as teaching that angiogenesis is "important in the

pathogenesis of atherosclerotic plaque" as it facilitates "the accumulation of atherosclerotic plaques". Respectfully, such an assertion does not accurately reflect the teachings of Pels et al.

Beginning on page 896, right column (under the heading "Functional Significance of Vasa Vasorum", Pels et al states that:

> "[e]ven though there are more vasa vasorum in diseased than in normal coronary arteries, the functional significance of these microvessels is unknown." (Underling added.)

In Figure 3 (page 896), Pels et al illustrates two different interpretations of the available data relating to the functional significance of coronary vasa vasorum. In "Concept I", intimal/medial microvessels grow inward "to nourish the expanding plaque" during the chronic process of atherogenesis. In "Concept II", adventitial microvessels form after acute coronary artery injury as a result of angiogenic stimuli - these microvessels are essential for the maintenance of arterial wall hemostasis during subsequent arterial repair.

On page 897, left column, Pels et al discusses "Concept I" in greater detail. There, reference is made to studies describing an "association" between

neovascularization of the intima and atherosclerosis. Pels et al concludes this section with the statement that it is likely that neovascularization plays a fundamental role in atherogenesis by nourishing the growing plaque but that "it is unknown if proliferation of the vasa vasorum precedes or follows plaque formation and luminal narrowing" (underlining added).

On page 897, right column, Pel et al summarizes the results of studies examining the role of adventitial microvessels and lesion formation. Certain of those studies demonstrated that obstruction of the vasa vasorum resulted in the formation of arterial lesions (see Nakata and Shionoya), others suggested that development of atherosclerotic lesions could be induced by disrupting adventitial microvessels (see Booth et al) and that maintenance of an arterial wall microcirculation may attenuate neointimal formation (see Barker et al).

At the top of page 899, right column, Pels et al states that:

> although the presence of microvessels in the plaque may be associated with the progression of disease, preservation of the arterial wall microcirculation may be required to prevent excessive tissue scarring and possible contracture.

(Underlining added.)

In discussing the functional significance of coronary vasa vasorum, Pels et al state:

> Newly formed adventitial vasa vasorum supply the increased arterial wall mass, thereby preventing fibrosis and maintaining arterial compliance. We hypothesize that an arterial wall rich in microvessels may prevent contracture and luminal narrowing. (See legend to Fig. 3 at page 896.)

In summarizing, Pels et al points out that the data emphasize the complexity of the role of vasa vasorum in atherogenesis and restinosis and that future studies "are required for a better understanding of the function of the arterial wall microcirculation in diseased arteries".

In view of the above, it will be apparent that Pels et al does not teach that angiogenesis "is important in the pathogenesis of atherosclerotic plaque", or that it is "known to facilitate the accumulation of atherosclerotic plaques" as the Examiner contends. Rather Pels et al teaches that there is an association between arterial wall microvessels and atherosclerotic plaques. Importantly, and as noted above, Pels et al states that it is unknown whether vessel proliferation precedes or follows plaque formation. Thus Pels et al cannot be interpreted as

teaching the importance of angiogenesis in pathogenesis, as the Examiner contends.

In view of the facts that: i) the teachings of Clark are limited to ocular neovascularization, and ii) Pels et al does not teach that angiogenesis is involved in the pathogenesis of atherosclerotic plaque, the Examiner's rejection of the claims as obvious must fail. Indeed, it is apparent that the rejection is not fairly based on what the cited references teach or would have suggested but rather on improper hindsight-based reasoning having in mind the present invention. Accordingly, reconsideration and withdrawal of the rejection are requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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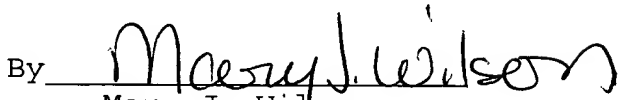
By 
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